Mechanism of the Decomposition of α-Aminothiol Esters[1,2]

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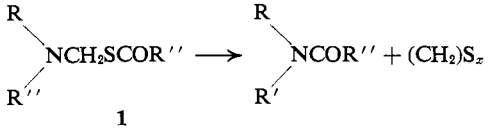
The question of whether the generally facile thermal decomposition of α-aminomethanethiol esters, forming amides and polythioformaldehyde, proceeds by an intramolecular route, involving a four-membered cyclic intermediate, or by a bimolecular route has been investigated by kinetic studies in various solvents and by a crossover experiment without solvent. The data obtained indicated that both of these mechanisms occur, the bimolecular process being predominant in nitromethane and chloroform solutions and in the neat liquids. In relatively inert solvents, such as n-hexane, acetone, and 1,2-dimethoxyethane, however, a significant amount of the decomposition proceeds by a kinetically first-order process, which seems likely to be the intramolecular path involving a four-membered cyclic intermediate. Other aspects of the reaction are also discussed, including catalysis by tertiary amines and the first-order reaction observed in acetonitrile.

The decomposition of α-aminothiol esters of type I to the corresponding amides and polythioformaldehyde was observed independently by Smissman and Sorenson[3] and by these authors.[4] The reaction has been found to be general for a variety of compounds



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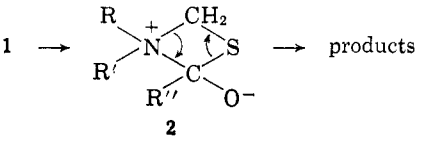
(**1**) having R as an alkyl group and R′ and R′′ either alkyl or phenyl groups, but the ease of the rearrangement varied considerably with structure.

It is of interest to compare this rearrangement with that of β- and γ-aminothiol esters, which is a simple S–N acyl migration, giving the corresponding β- and γ-acylaminothiols.[5,6] Although there are some obvious differences in the two rearrangements, such as the requirement of a hydroxylic solvent with acidic or basic catalysis for the β and γ series (conditions which simply give hydrolysis with α-aminothiol esters), it would seem reasonable that they might be somewhat similar mechanistically, with the reaction in each case beginning with nucleophilic attack of the amino nitrogen atom on the carbonyl carbon atom.

Convincing evidence has been presented recently for the intramolecular nature of the β- and γ-aminothiol ester rearrangement, involving formation of a 1,3-thiazolidine intermediate and several equilibria of protonated forms, with final ring cleavage between the sulfur atom and the original carbonyl carbon atom, to give the product.[7] An intramolecular mechanism, involving formation of a 1,3-thiazetidine intermediate, was recently suggested by Smissman and Sorenson[3] for the α-aminothiol ester rearrangement, and also was



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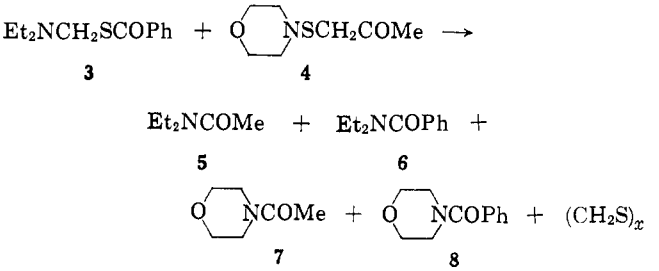
given serious consideration in our work, since cleavage of opposite bonds in the four-membered ring in **2** would give the observed product without acidic or basic catalysis. A similar mechanism has been suggested by Tarbell and Scharrer[8] for the uncatalyzed decomposition of mixed carboxylic–dithiocarbamic anhydrides to amides and carbon disulfide, but no evidence was available to support it. The probable relationship of that reaction and perhaps others to the decomposition of α-aminothiol esters gave added interest in studying the latter.

There are, of course, other possible mechanisms for the decomposition of α-aminothiol esters, including analogous noncyclic and bimolecular processes, and to check the validity of the intramolecular mechanism, a crossover experiment was performed with two α-aminothiol esters which decompose at about the same rate. An equimolecular mixture of N,N-diethylaminomethanethiol benzoate (**3**) and 1-morpholinomethanethiol acetate (**4**) was heated without solvent at 65°. The amide product obtained by the usual method of processing was found to be a mixture of all four possible



amides, (**5**–**8**). Their amounts were determined by gas chromatographic analysis to be in the molecular ratio of 15:30:36:19 for **5**:**6**:**7**:**8**, and it was demonstrated that acyl exchange did not occur between the two unmixed products, **6** and **7**, either during the heating or the gas chromatographic analysis. The slight deviation of the amounts of products from being exactly equimolar is not significant, particularly because some of

(1) Presented at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 9, 1965, and in part at the Kansas City Chemistry Conference, Kansas City, Mo., Nov., 20, 1964. This work will be included in the Ph.D. Dissertation of S. N. at Kansas State University.

(2) Support of this work by National Institutes of Health Research Grant R.H-00300-02 is gratefully acknowledged.

(3) E. E. Smissman and J. R. J. Sorenson, *J. Org. Chem.*, 30, 300 (1965).

(4) S. Searles, Jr., S. Nukina, and E. R. Magnuson, *ibid.*, 30, 1920 (1965).

(5) T. Wieland and E. Bokelmann, *Ann.*, **576**, 20 (1952).

(6) T. Wieland and H. Hornig, *ibid.*, 600, 12 (1956).

(7) R. B. Martin and R. I. Hedrick, *J. Am. Chem. Soc.*, **84**, 106 (1962).

(8) D. S. Tarbell and R. P. F. Scharrer, *J. Org. Chem.*, 27, 1972 (1962).

6 and 7 were present initially, due to some decomposition of 3 and 4 having unavoidedly occurred before mixing; and it can be concluded that a bimolecular pathway must be the predominant one for the decomposition of such α-aminothiol esters without solvent.

A kinetic study was then carried out on the reaction in nitromethane solution, for it proceeded cleanly and in good yield in that solvent and could be followed titrimetrically with precision. The amount of unreacted aminothiol ester was determined by titration with perchloric acid. The reaction could be followed also by the change in n.m.r. and infrared spectra, these methods giving confirming but less precise results.

The data obtained showed a linear, second-order kinetic relationship, as indicated in Figure 1, for the five α-aminothiol esters investigated. The second-order rate constants, which are listed in Table I, diminished regularly with increasing bulk of the N-alkyl group, and the benzoate ester of N,N-diethylaminomethanethiol had a significantly lower rate constant than the corresponding acetate ester. These substituents suggest that the rate-determining step is an attack of the amino nitrogen atom on the carbonyl carbon atom, since steric hindrance at these sites decreased the rate of reaction.[9]

Table I. Second-Order Rate Constants for Nitromethane Solutions at 27°

Ester	k_2, l./mole hr.
$Me_2N-CH_2S-CO-Me$	2.6
$(CH_2)_5N-CH_2S-CO-Me$	1.1
$Et_2N-CH_2S-CO-Me$	0.21
$i\text{-}Pr_2N-CH_2S-CO-Me$	0.064
$Et_2N-CH_2-S-CO-Ph$	0.069

Very similar substituent effects were observed for the decomposition of α-aminothiol esters without solvent. Thus, N,N-dimethylaminomethanethiol acetate decomposed completely to N,N-dimethylacetamide and thioformaldehyde in 24 hr. at 70°, while the corresponding diethylamino compound required about 15 hr. at 70° and the diisopropylamino analog was less than half decomposed after 40 hr. at 100°.[4] The low rates of decomposition for morpholinomethanethiol acetate and N-methylanilinomethanethiol acetate[4] can be ascribed to relatively low nucleophilic character of the nitrogen atoms in these molecules, since morpholine and N-methylaniline are considerably weaker bases than dimethylamine and diethylamine.[10-12] The lower rate of benzoate esters relative to acetate esters was also observed in the decompositions that were carried out without solvent.[4]

These data thus are consistent with the rate-determining step for the decomposition being a bimolecular process involving nucleophilic attack of the amino

(9) The slower rates observed for the aminolysis and hydrolysis of alkyl benzoates, relative to the corresponding acetates, by R. Schwyzer, *Helv. Chim. Acta*, 36, 414 (1953), provides an analogy.
(10) H. K. Hall, *J. Am. Chem. Soc.*, 79, 5441 (1957).
(11) J. N. Pring, *Trans. Faraday Soc.*, 19, 717 (1923).
(12) J. O. Edwards, *J. Am. Chem. Soc.*, 76, 1540 (1954), and 78, 1819 (1956), has presented a relationship between nucleophilicity and basicity and polarizability.

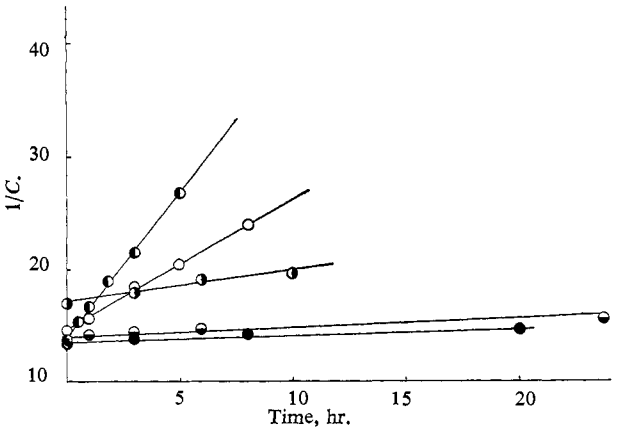
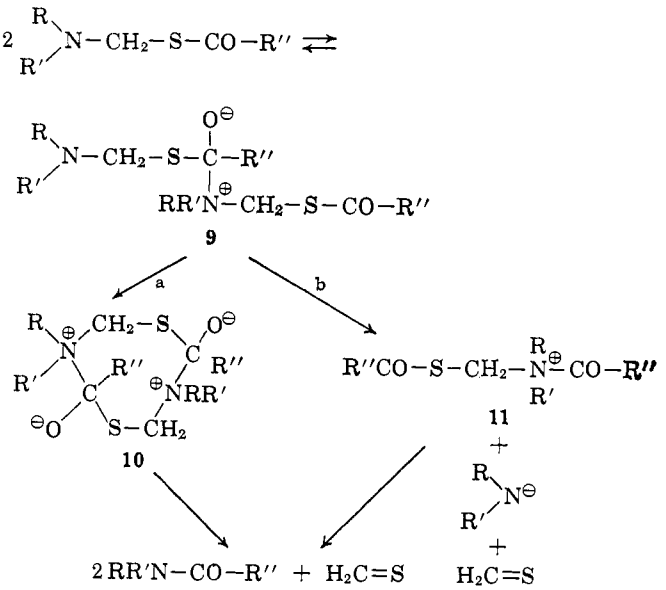


Figure 1. Second-order plot for decomposition of α-aminothiol esters in nitromethane at 27°: ◐, Me_2NCH_2SCOMe; ○, $(CH_2)_5NCH_2SCOMe$; ◑, Et_2NCH_2SCOMe; ◒, $i\text{-}Pr_2NCH_2SCOMe$; ●, $Et_2NCH_2SCOC_6H_5$.

nitrogen atom on the carbonyl carbon atom of another aminothiol ester molecule. The dipolar intermediate **9** might decompose (a) by a concerted process involving an eight-membered cyclic intermediate **10**, or (b) by direct elimination of an α-aminomercaptide ion, which would be unstable, decomposing rapidly to thioformaldehyde and the substituted amide ion **11**.[13] It is



difficult to distinguish between these two routes of decomposition of **9** at present. In favor of route a is the known tendency for cyclization of eight-membered rings containing α-aminomethanethiol units,[14,15] while for the suggested route b, it can be said that the amide ion formed must react rapidly with the amide ion, the other ionic fragment, for otherwise it or the corresponding secondary amine would compete favorably with unreacted α-aminothiol ester for the carbonyl sites. Such a situation would result in a chain reaction, which would not show second-order kinetics as found.

Addition of a free amine to a solution of an α-aminomethanethiol ester was found indeed to result in a rapid

(13) Unpublished observations in this laboratory.
(14) T. W. Campbell, *J. Org. Chem.*, 22, 569 (1957).
(15) N. J. Leonard, K. Conrow, and A. E. Yethon, *ibid.*, 27, 2019 (1962).

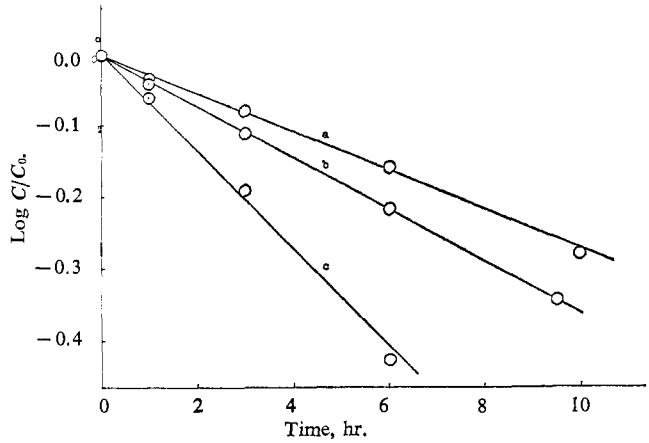


Figure 2. First-order plot for decomposition of N,N-diethylaminomethanethiol acetate in nitromethane solutions containing pyridine in concentrations 0.080 (a), 0.106 (b), and 0.209 *M* (c), at 27°.

reaction of the latter with the amine. Thus, N,N-diethylaminomethanethiol acetate reacted readily with 1 mole of dimethylamine in carbon tetrachloride at room temperature to form dimethylacetamide, which was isolated in 83% yield. This result correlates with the much greater basicity of dimethylamine over the α-aminothiol ester,[13] which would be expected to give it greater nucleophilicity.[12]

When the amine added was tertiary, as in the case of pyridine and triethylamine, it acted as a strong catalyst for the decomposition of the α-aminothiol ester to amide and polythioformaldehyde. Under such conditions, the kinetic order with respect to the ester was first order, and the reaction rate constant was proportional to the tertiary amine concentration, as shown in Figure 2. This result is consistent with the added tertiary amine reacting with the ester carbonyl carbon atom. The initial adduct in this case would decompose to thioformaldehyde, an amide ion, and an acylammonium ion, a well-known acylating agent which would rapidly acylate the amide ion.

$$R_2NCH_2SCOR' + R''_3N \longrightarrow R_2NCH_2S\underset{\oplus NR''_3}{\overset{O\ominus}{\underset{|}{\overset{|}{C}}}}R' \longrightarrow$$

$$R_2N\ominus + H_2C{=}S + R''_3\overset{\oplus}{N}COR' \longrightarrow R_2NCOR' + H_2C{=}S + R''_3N$$

The dipolar character of the initial adduct **9** formed in the proposed rate-determining step in the bimolecular mechanism proposed, would imply that a large solvent effect might be observed. This expectation was confirmed by the observation of very slow rates of decomposition of α-aminothiol esters in *n*-hexane, and of rates of intermediate magnitude in certain solvents of intermediate dielectric constant, such as acetone and 1,2-dimethoxyethane.

In these and other solvents, however, the kinetic order of the reaction was different from that which had been observed in nitromethane. The reaction in acetone, 1,2-dimethoxyethane, *n*-hexane, and chloroform gave rate data which fitted concurrent first- and second-order processes, while in acetonitrile the reaction appeared to be entirely first order. In fact, the occurrence of a first-order process could be demonstrated in nitromethane, also, by studying very low concentrations of the α-aminothiol ester, but in nitromethane the first-order rate constant (k_1) was relatively low compared to the second-order constant (k_2) (see Table II). These kinetic studies were carried out with N,N-diethylaminomethanethiol acetate, a typical α-aminothiol ester, excepting the rate measurements in *n*-hexane, where the rate was immeasurably slow for this ester and the more readily decomposed N,N-dimethylaminomethanethiol acetate was studied. Determination of the reaction rates in *n*-hexane and in acetonitrile solution from spectral data agreed well with the values obtained from titration data.

Table II. Rate Constants for the Decomposition of α-Aminothiol Esters

Solvent	Temp., °C.	$k_1 \times 10^3$, hr.$^{-1}$	$k_2 \times 10^3$, l./mole hr.
Et_2N–CH_2S–CO–Me			
Nitromethane	27	5.2	180
Acetonitrile	27	11	0.5
Chloroform	50	2.3	62
Acetone	50	9.8	12
1,2-Dimethoxyethane	50	4.9	4.9
n-Hexane	50	(Too small to measure)	
Me_2N–CH_2S–CO–Me			
n-Hexane	50	0.7	2.5

The first-order reaction thus observed cannot, of course, be automatically identified with the unimolecular, cyclic process under consideration, since there are other possibilities for the same kinetic order. Nucleophilic attack of the solvent on the ester would give first-order kinetics, similar to the case of pyridine catalysis, and this may well be the case with acetonitrile. The fact that the reaction rate is not much greater in acetonitrile than in nitromethane may be due to the better electron-acceptor ability of nitromethane in hydrogen bonding, which would polarize the ester carbonyl group, making it more susceptible to nucleophilic attack by the amino nitrogen atom, and would also stabilize the dipolar intermediate (**9**) formed.

Similar effects of hydrogen bonding would be expected with chloroform, but the much lower dielectric constant of chloroform (4.8 at 20°, compared to 37.5 for acetonitrile and for nitromethane at the same temperature[16]) would be less favorable to the dipolar intermediate in either the cyclic unimolecular process or the bimolecular process. Probably as a result mainly of the dielectric constant difference, the over-all reaction rate is much lower in chloroform than in nitromethane. It may be significant, however, that the second-order rate constant in chloroform is much larger than that in acetone, which has a dielectric constant of 21.2 at 20°[16] but is a poor electron donor in hydrogen bonding. Another effect of such hydrogen-bonding ability of the solvent might be to abstract the dialkylamide ion from the solvent cage, if the bimolecular adduct **9** decomposes by the noncyclic process b; such an action would lead to chain character of the reaction, with an observed rate order approaching unity. It is difficult to

(16) A. A. Maryott and E. R. Smith, U. S. National Bureau of Standards Circular No. 514, 1951.

Table III. Rearrangement of α-Aminothiol Esters in Nitromethane

Ester	Concn., %	Temp., °C.	Time, hr.	Amide formed	Yield, %	B.p., °C. (mm.)	n_D (°C.)
Et_2N-CH_2SAc	4.6	90	5	$Et_2N-CO-Me$	51	80 (20)	1.4400 (30)
$O(CH_2)_4N-CH_2-SAc$	25	70	20	$O(CH_2)_4N-CO-Me$	74	111–112 (10)	1.4840 (20)
$(CH_2)_5N-CH_2-SAc$	25	70	12	$(CH_2)_5N-CO-Me$	92	120–122 (30)	1.4788 (27)

say whether the small amount of first-order process apparently observed in nitromethane and chloroform may be due to such a chain process occurring.

Since *n*-hexane, acetone, and 1,2-dimethoxyethane, however, are very weak electron acceptors and also have very weak nucleophilic properties, such solvent effects would not be expected to be very pronounced for them. It seems likely, therefore, that the first-order reaction in these solvents is the cyclic, unimolecular process involving formation of a 1,3-thiazetidine intermediate (2). The first-order rate constant for N,N-diethylaminomethanethiol acetate in acetone and 1,2-dimethoxyethane was about the same as the second-order rate constant, while the first-order rate constant for the N,N-dimethyl analog in *n*-hexane was about one-third that of the second-order constant. The difference may reflect the greater steric hindrance of the N-alkyl groups in intermolecular reactions than in intramolecular reactions.

Thus, it appears that the unimolecular, cyclic mechanism for the decomposition of α-aminothiol esters may occur in inert solvents, accompanied by its bimolecular counterpart, but the latter tends to predominate in concentrated solutions, including the neat liquids, and in hydrogen-bonding solvents.

Experimental Section

Crossover Experiment. An equimolar mixture of N,N-diethylaminomethanethiol benzoate and 1-morpholinomethanethiol acetate were heated at 65° for 30 hr. The precipitated polythioformaldehyde was removed by filtration, and the residue was analyzed by gas chromatography, using a silicon–Fluoropak column. Four peaks, with intensity ratios 15:36:30:19, and with retention times identical with those of diethylacetamide, acetylmorpholine, diethylbenzamide, and benzoylmorpholine, were observed. Diethylacetamide and benzoylmorpholine, the crossover products, were checked further by collection from the gas chromatographic column. Diethylacetamide had b.p. 82–85° (20 mm.) and an infrared spectrum identical with an authentic sample, and the benzoylmorpholine was recrystallized from petroleum ether (b.p. 65–70°), m.p. and m.m.p., 73.5–74°.[17]

A mixture of acetylmorpholine and diethylbenzamide gave the same two peaks and no additional peaks in the gas chromatograph before and after heating at 65° for 30 hr.

Decomposition of N,N-Dimethylaminomethanethiol Acetate without Solvent. The conditions given for the decomposition of this compound in Table II of ref. 4 were much more rigorous than necessary. Actually, the decomposition to form N,N-dimethylacetamide and thioformaldehyde was practically complete after 2 hr. at 70°, as shown by infrared and n.m.r. spectra.

(17) G. F. McCasland and E. O. Horswill, *J. Am. Chem. Soc.*, 73, 3923 (1951).

Decomposition of α-Aminothiol Esters in Nitromethane. A solution of 0.97 g. of N,N-diethylaminomethanethiol acetate in 20 g. of nitromethane was heated slightly, an exothermic reaction starting immediately, and the reaction mixture was maintained at 90° for 5 hr. After removal of the nitromethane by distillation, fractional distillation *in vacuo* gave 0.35 g. of N,N-diethylacetamide, b.p. 80° (20 mm.), $n^{30}D$ 1.4400 (lit. b.p. 90–91° (30 mm.),[18] $n^{17.6}D$ 1.4412[19]). Its infrared spectrum was identical with that of an authentic sample of N,N-diethylacetamide. There was no evidence for any other product, except polythioformaldehyde, which remained as a distillation residue.

1-Morpholinomethanethiol acetate and 1-piperidinomethanethiol acetate were treated similarly, except that the thioformaldehyde was removed by filtration prior to distillation. The results with these three compounds, which are summarized in Table III, were comparable to those previously obtained when the decomposition was carried out without solvent.

Kinetic Study of the Rearrangement. A. Titrimetric Method. The change in the concentration of α-aminothiol esters was followed by titration of aliquot samples, diluted with equal volumes of ethanol, with 0.2 *N* perchloric acid, methyl orange being used as indicator. Typical data obtained are listed in Table IV.

B. Ultraviolet Spectral Method. The change of intensity of the absorption at 227 mμ, which is in an absorption band no doubt due to the thiol ester grouping, was followed in a 1-mm. cell by means of a Cary Model 11 spectrophotometer. This method could be applied to solutions in *n*-hexane and acetonitrile, which were practically transparent in this region, and the rate constants obtained agreed well with those obtained by the titrimetric method, as shown in Table IV.

C. N.m.r. Method. The decrease of the singlet peak at δ 4.45 observed in N,N-diethylaminomethanethiol acetate in nitromethane solution at 70°. This absorption is due to the methylene hydrogen atoms between the sulfur and nitrogen atoms in the α-aminothiol ester[4] and completely disappears during the decomposition reaction. The areas of the peak at different times were measured by the weights of paper cutouts of same size and shape and were, of course, proportional to the corresponding concentrations of the ester. The plot of time *vs.* $1/C$ gave a better linear plot than that the plot of time *vs.* log C/C_0, suggesting second-order kinetics, but the precision was not great enough to warrant calculation of a rate constant.

D. Calculation of rate constants in cases where both first- and second-order processes occurred, was made by means of the equation

(18) S. Stephanou, C. A. VanderWerf, and H. H. Sisler, *ibid.*, 70, 265 (1948).

(19) K. von Awers, *Z. physik. Chem.*, **147**, 458 (1930).

Table IV. Some Observed Rates of Decomposition of α-Aminothiol Esters

Solvent	Temp., °C.	Method	Rate × 10^3, mole/l. hr.
		$Et_2N-CH_2S-CO-Me$	
Nitromethane	27	Titration	17.4 at 0.30 *M*
Nitromethane	27	Titration	1.10 at 0.060 *M*
Nitromethane	27	Titration	0.492 at 0.040 *M*
Acetonitrile	27	Titration	0.525 at 0.050 *M*
Acetonitrile	27	Ultraviolet	0.0525 at 0.005 *M*
Chloroform	50	Titration	1.25 at 0.30 *M*
Chloroform	50	Titration	0.101 at 0.040 *M*
Acetone	50	Titration	3.18 at 0.25 *M*
Acetone	50	Titration	0.304 at 0.030 *M*
1,2-Dimethoxyethane	50	Titration	1.43 at 0.30 *M*
1,2-Dimethoxyethane	50	Titration	0.205 at 0.04 *M*
n-Hexane	50	Titration and ultraviolet	Too small to measure
		$Me_2N-CH_2S-CO-Me$	
n-Hexane	50	Titration	6.04 at 1.50 *M*
n-Hexane	50	Titration	0.664 at 0.40 *M*
n-Hexane	50	Ultraviolet	6.67 at 1.4 *M*
n-Hexane	50	Ultraviolet	0.736 at 0.40 *M*

$$\text{rate} = k_1C + k_2C^2$$

where C is the molar concentration of the α-aminothiol ester, and the rates were in the units, mole/l. hr., taken as the tangents of the plots of such rates *vs.* concentration. Simultaneous equations were then solved for rates at different concentration in the same solvent. Typical over-all rate data used are listed in Table IV, each entry being for a separate run, and the first- and second-order rate constants calculated are given in Table II.

E. Effect of Light. Since it was convenient to carry out these studies with laboratory illumination, the possibility of a catalytic affect of light was investigated. The rate of decomposition of N,N-diethylaminomethanethiol acetate was followed by the titration method in a dark room and in the laboratory with the usual illumination. The rates, however, were essentially the same: at 0.30 *M* concentration, the rate was 1.7×10^{-2} mole/l. hr. in both light and dark for nitromethane solutions at 27°, and 3.9×10^{-3} and 4.4×10^{-3} in the light and dark, respectively, for acetone solutions at 50°. The latter difference is approximately the magnitude of the possible experimental error.

Therefore, it was concluded that moderate illumination did not affect the rates of decomposition. Under strong sunlight or mercury-arc illumination, N,N-diethylaminomethanethiol in ethyl ether solution was observed to be converted slowly into a resinous product, but this type of reaction would not appear to be important in the present study.

Catalysis by Tertiary Amines. To a solution of 0.80 g. of N,N-diethylaminomethanethiol acetate in 80 ml. of nitromethane was added a small amount of pyridine or triethylamine. The concentration of the ester was determined by titration with 0.2 *N* perchloric acid of an aliquot of the solution before addition of the amine, and the amine concentration was determined by titration of an aliquot of the solution after addition of the amine and subtraction of the original titer, with adjustment for volume change. The change in the α-aminothiol ester concentration at 27° then was followed by titration with 0.2 *N* perchloric acid, methyl orange being used as the indicator. The results obtained are summarized in Table V.

Table V. Rate Constants for the Decomposition of N,N-Diethylaminomethanethiol Acetate in Nitromethane Solutions Containing a Tertiary Amine

Amine	Amine concn., *M*	k_1, hr.$^{-1}$	k_1/amine concn., l./mole hr.
Pyridine	0.080	0.065	0.81
Pyridine	0.106	0.085	0.80
Pyridine	0.209	0.16	0.77
Triethylamine	0.116	0.061	0.53

Reaction of Diethylaminomethanethiol Acetate with Dimethylamine. A. In Ether–Carbon Tetrachloride Solution. A solution of 8.05 g. (0.05 mole) of diethylaminomethanethiol acetate and 2.25 g. (0.05 mole) of dimethylamine in 30 ml. of carbon tetrachloride and 70 ml. of ether (added to prevent formation of two layers) was kept at room temperature for 10 hr. Hydrogen chloride gas then was bubbled in to precipitate any free amine; the white precipitate which formed was removed by filtration and identified as diethylamine hydrochloride by its melting point of 210–215° (lit.[20] m.p. 216°), neutralization equivalent of 110 (calculated neut. equiv. 109.5), and the melting point of the *p*-toluenesulfonamide of 59–60° (lit.[21] m.p. 60°). The yield was 1.3 g. (24%).

Distillation of the filtrate gave 2.95 g., b.p. 66–67° (21 mm.), identified as dimethylacetamide from the boiling point, infrared spectrum, and refractive index ($n^{27}D$ 1.4372); 1.30 g., b.p. 73–75° (21 mm.), shown by n.m.r. and gas chromatography to be an equimolar mixture of dimethylacetamide and diethylacetamide; 0.59 g. of a basic substance, b.p. 50–88° (0.5 mm.), not identified as yet; and 1.20 g. of residue, identified as polythioformaldehyde from its infrared spectrum.

(20) O. Wallach, *Ann.*, **214**, 275 (1882).
(21) W. Marckwald and A. F. von Droste-Huelshoff, *Ber.*, **31**, 3263 (1898).

The combined yield of dimethylacetamide was 3.60 g. (83%), and the yield of diethylacetamide was 0.65 g. (11%).

B. In Nitromethane Solution. The decrease in amine content was followed in a solution of 1.1365 g. of diethylaminomethanethiol acetate and 0.300 g. of diethylamine in 100 ml. of nitromethane solution. The concentrations were determined as described above under Catalysis by Pyridine. The reaction followed second-order kinetics (first with respect to ester and to amine) in the early part of the reaction, and the rate constant was 0.0707 l./mole min.

Sulfoxide–Carbodiimide Reactions. I. A Facile Oxidation of Alcohols

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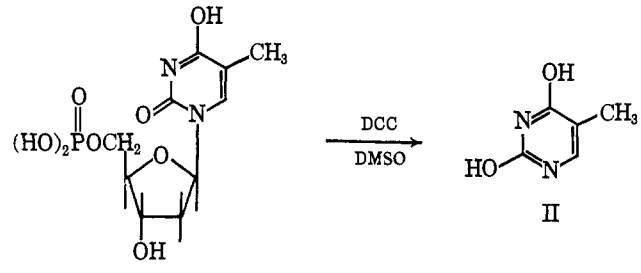
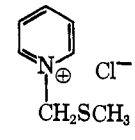
The reaction of thymidine 5′-phosphate with dicyclohexylcarbodiimide (DCC) in dimethyl sulfoxide (DMSO) leads to rapid cleavage of the N-glycosidic bond and release of thymine. This glycosidic cleavage is found to be typical of nucleotide derivatives containing a free 3′-hydroxyl group and also occurs with free 3′-hydroxyl-containing nucleosides in the presence of anhydrous phosphoric acid. Such a reaction applied to 3′-O-acetylthymidine leads to the formation of 3′-O-acetylthymidine-5′-aldehyde which was isolated as its crystalline dinitrophenylhydrazone. The cleavage of the N-glycosidic bond in nucleosides is explained by oxidation of the 3′-hydroxyl group to a ketone followed by spontaneous β-elimination of the heterocyclic base. The general reaction of alcohols with DMSO and DCC in the presence of certain acids has been found to lead to efficient oxidation to the corresponding aldehydes or ketones under extremely mild conditions. Optimal conditions for the oxidation of testosterone to Δ⁴-androstene-3,17-dione have been determined, and it is concluded that this reaction is most advantageously carried out using 0.5 molar equiv. of pyridinium trifluoroacetate and 3 molar equiv. of DCC in DMSO or mixed solvents containing DMSO at room temperature. A mechanism for the reaction is proposed.

Recently, we have had occasion to investigate the feasibility of phosphorylating an alcohol by the cyanoethyl phosphate–dicyclohexylcarbodiimide method,[2] using dimethyl sulfoxide (DMSO) as the solvent rather than pyridine. As a test we attempted the phosphorylation of 2′,3′-O-isopropylideneuridine and were surprised to find that the presence of even 10% anhydrous DMSO in pyridine completely prevented the formation of any phosphorylated nucleoside as demonstrated by paper electrophoresis. As a further test we attempted the carbodiimide-promoted polymerization of thymidine 5′-phosphate (I),[3] once again using anhydrous DMSO rather than pyridine as the reaction medium. The reaction in DMSO, unlike that in pyridine, rapidly became colored and emitted a foul, sulfide-like smell. Chromatographic examination after various times showed that within 15 min. the nucleotide had completely degraded to thymine (II) with cleavage of the N-glycosidic bond. The crystalline thymine was isolated almost quantitatively from the reaction by ion-exchange chromatography and identified by ultraviolet and infrared spectroscopy as well as by paper and thin layer chromatography.



I II

A second product, in much lower yield, was also formed if excess pyridine was present in the reaction. This was found by ultraviolet spectroscopy to be an N-substituted pyridinium compound, this structure being supported by paper electrophoresis which showed it to have a single positive charge both at pH 3 and 8. A small amount of this material was isolated chromatographically from a pyridine-containing reaction and shown to have the structure III by nuclear magnetic resonance spectroscopy and comparison with an authentic sample prepared from pyridine and chloromethyl methyl sulfide. The possible implications of presence of this by-product will be discussed later.



III

Cleavage of thymidine 5′-phosphate to thymine was also observed in similar reactions using the free acid and tributylammonium salt forms of the nucleotide. Using the free acid, quantitative cleavage to thymine occurred very rapidly but with the trialkylamine salts the reaction was slow and after 18 hr. consider-

(1) Syntex Postdoctoral Fellow, 1961–1963.
(2) G. M. Tener, *J. Am. Chem. Soc.*, 83, 159 (1961).
(3) G. M. Tener, H. G. Khorana, R. Markham, and E. H. Pol, *ibid.*, 80, 6223 (1958).